Answer 1:

**Bibliographic Information**

**S-phase checkpoints regulate Apo2 ligand/TRAIL and CPT-11-induced apoptosis of prostate cancer cells.** Ray, Subrata; Shyam, Sunitha; Fraizer, Gail C.; Almasan, Alexandru. Department of Cancer Biology, Lerner Research Institute, Cleveland, OH, USA. Molecular Cancer Therapeutics (2007), 6(4), 1368-1378. Publisher: American Association for Cancer Research, CODEN: MCTOCF ISSN: 1535-7163. Journal written in English. CAN 147:22986 AN 2007:412515 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

As S-phase checkpoints play crit. roles in maintaining genomic integrity and replicating the human genome correctly, understanding the mol. mechanism by which they regulate the therapeutic response is of great interest. Previously, we reported that the cytotoxic effect of a zinc-bound form of Apo2 ligand/tumor necrosis factor-related apoptosis-inducing ligand (Apo2L/TRAIL), which is currently evaluated in clin. trials, in combination with low-dose CPT-11, induces apoptosis of C4-2 human prostate cancer cells and tissues. Here, we show that apoptosis, induced synergistically by this combination treatment, was assocd. with accumulation of cells in early S phase, indicated by cell cycle analyses, increased proliferating cell nuclear antigen, and Chk2-Thr68 phosphorylation in tumors xenografted in mice. The combination treatment induced an S-phase checkpoint response through activation of Chk2 and Chk1 by the ataxia telangiectasia mutated and ataxia telangiectasia mutated and Rad3 related kinases, leading to phosphorylation and decreased Cdc25A levels. Cdc25A-dependent regulation of cyclin-dependent kinase 2 (Cdk2) and changes in assocn. of p21WAF1/CIP1 and hSpy1 with Cdk2 resulted in inhibition of Cdk2-assocd. kinase activity. Knockdown of ataxia telangiectasia mutated/Chk2 and ataxia telangiectasia mutated and Rad3 related/Chk1 by small inhibitory RNAs abrogated the S-phase checkpoint and accelerated apoptosis, resulting in caspase-3 activation and poly(ADP-ribose) polymerase 1 cleavage following combination treatment. Thus, Apo2L/TRAIL + CPT-11 treatment-induced apoptosis is regulated through an S-phase checkpoint controlled by the Chk2-Cdc25A and Chk1-Cdc25A pathways and inhibition of Cdk2-assocd. kinase activity. Low-dose CPT-11 and aphidicolin increased the proportion of S-phase cells and sensitized cells to Apo2L/TRAIL, by inducing phosphatidylserine externalization, caspase activation, and poly(ADP-ribose) polymerase 1 cleavage.

Combinations with S-phase arrest-inducing chemotherapeutic drugs may represent promising avenues for clin. development of Apo2L/TRAIL. [Mol Cancer Ther 2007;6(4):1368-78].

Answer 2:

**Bibliographic Information**

**Ribonucleotide reductase inhibitors enhance cidofovir-induced apoptosis in EBV-positive nasopharyngeal carcinoma xenografts.** Wakisaka, Naohiro; Yoshizaki, Tomokazu; Raab-Traub, Nancy; Pagano, Joseph S. Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC, USA. International Journal of Cancer (2005), 116(4), 640-645. Publisher: Wiley-Liss, Inc., CODEN: IJCNAW ISSN: 0020-7136. Journal written in English. CAN 143:278635 AN 2005:781608 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

In nasopharyngeal carcinoma (NPC), Epstein-Barr virus (EBV) infection is mainly latent, and the tumor cells contain episomal viral DNA. We have shown that the acyclic nucleoside phosphonate analog, cidofovir [(S)-1-(3-hydroxy-2-(phosphonylmethoxypropyl)cytosine)] (HPMPC), inhibits growth of NPC xenografts in nude mice by causing apoptosis. The ribonucleotide reductase (RR) inhibitors, hydroxyurea and didox (3,4-dihydroxybenzohydroxamic acid), have been demonstrated to inhibit neoplastic growth and are used as antiviral and anticancer agents. Here we show that RR inhibitors enhance the antitumor effect of cidofovir in EBV-transformed epithelial cells. MTT assays indicate that hydroxyurea and didox enhance cidofovir-induced cell toxicity in NPC-KT cells, an EBV-pos. epithelial cell line derived from NPC. The effect is due to enhancement of apoptosis through the caspase cascade as shown by pronounced cleavage of poly(ADP-ribose) polymerase. Finally, hydroxyurea strikingly enhanced the cidofovir-induced growth-inhibitory effect on NPC grown in athymic mice. The results suggest that RR inhibitors should enhance the antitumor effect of acyclic nucleoside phosphonate analogs on NPC.

Answer 3:

**Bibliographic Information**

**Gene expression in intrahepatic tumors through DNA recombination by a replication-activated adenovirus vector.** Huang, Xiao W.; Lieber, Andre; Tang, Zhao Y.; Lawrence, Theodore S.; Moyer, Mary P.; Zhang, Ming. Department of Radiation Oncology, University of Michigan, Ann Arbor, MI, USA. Cancer Gene Therapy (2004), 11(6), 450-456. Publisher: Nature Publishing Group, CODEN: CGTHEG ISSN: 0929-1903. Journal written in English. CAN 141:99222 AN 2004:449282 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

One strategy for improving selectivity of gene therapy is the use of a replication-activated adenovirus vector that mediates transgene expression specifically in tumor cells through homologous recombination of viral genomes. In this study, we compared replication-activated adenovirus contg. inverted repeats (Ad.IR-BG) with IR-deficient virus (Ad.BG) for selective gene expression in hepatocellular carcinoma and colon carcinoma metastases in the liver. We found that Ad.IR-BG conferred specific gene expression in both carcinoma cells, with minimal expression in hepatocytes and colon epithelial cells. This occurred through viral DNA recombination in Ad.IR-BG-infected tumor cells but not in normal cells. Hydroxyurea, which blocks DNA replication, inhibited DNA recombination and β-gal expression in Ad.IR-BG-infected but not Ad.BG-infected tumor cells. Finally, systemic injection of Ad.IR-BG into tumor xenografts in nude mice significantly improved selectivity of gene expression in tumors with minimal expression in normal tissues. Viral DNA recombination, which was absent in normal liver, was detected in Ad.IR-BG-infected tumors but not in Ad.BG-infected tissue. These findings demonstrated that replication-activated adenovirus can mediate tumor-specific gene expression through viral DNA recombination, which is otherwise deficient in normal cells.

Answer 4:

**Bibliographic Information**

**Novel Mode of Action of Tylophorine Analogs as Antitumor Compounds.** Gao, Wenli; Lam, Wing; Zhong, Sanbao; Kaczmarek, Conrad; Baker, David C.; Cheng, Yung-Chi. Department of Pharmacology, Yale University School of Medicine, New Haven, CT, USA. Cancer Research (2004), 64(2), 678-688. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 140:280770 AN 2004:64233 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

Tylophorine and its analogs are phenanthroindolizidine alkaloids, several of which have been isolated from the Tylophora genus of plants. Evaluation of (+)-S-tylophorine [DCB-3500 (NSC-717335)] and its analog DCB-3503 (NSC-716802) in the National Cancer Institute tumor screen showed a fairly uniform and potent inhibition of cell growth in all 60 cell lines (GI50 .apprx.10-8 M). To further evaluate the antitumor potential of these compds., we synthesized four tylophorine analogs, designated DCB-3500, DCB-3501, DCB-3502, and DCB-3503. All four tylophorine analogs exerted potent growth-inhibitory effects against HepG2, a human hepatocellular carcinoma cell line, and KB, a human nasopharyngeal carcinoma cell line. HepG2 cells were more sensitive than KB in terms of loss of clonogenicity. KB variants, which are resistant to etoposide, hydroxyurea, or camptothecin, have similar sensitivities to the tylophorine analogs, as do the parental KB cells. Treatment of nude mice bearing HepG2 tumor xenografts by i.p. injections of DCB-3503 at 6 mg/kg every 8 h on days 0 and 3 resulted in significant tumor growth suppression ($P < 0.0001$). Unlike conventional antitumor drugs, 3 μM DCB-3503 did not cause DNA breaks or apoptosis in HepG2 cells. Tylophorine analogs induced albumin expression and decreased α-fetoprotein expression in HepG2 cells, which suggests that tylophorine analogs could induce HepG2 differentiation. Tylophorine analogs had an inhibitory effect on cAMP response elements, activator protein-1 sites, or nuclear factor-κB binding site-mediated transcriptions. In summary, these tylophorine analogs are a unique class of antitumor compds. that have a mode of action different from known antitumor drugs.

Answer 5:

**Bibliographic Information**

**Cotylenin A, a Differentiation-inducing Agent, and IFN-α Cooperatively Induce Apoptosis and Have an Antitumor Effect on Human Non-Small Cell Lung Carcinoma Cells in Nude Mice.** Honma, Yoshio; Ishii, Yuki; Yamamoto-Yamaguchi, Yuri; Sassa, Takeshi; Asahi, Ken-Ichi. Saitama Cancer Center Research Institute, Yamagata University, Saitama, Japan. Cancer Research (2003), 63(13), 3659-3666. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 139:358205 AN 2003:505892 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

Cotylenin A, a novel inducer of the differentiation of leukemia cells, and IFN-α synergistically inhibited the growth of and induced apoptosis in several human non-small cell lung carcinoma cell lines. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and its receptor DR5 were the early genes induced by the combination of cotylenin A and IFNα in lung carcinoma cells. Neutralizing antibody to TRAIL inhibited apoptosis, suggesting that cotylenin A and IFNα cooperatively induced apoptosis through the TRAIL signaling system. This combined treatment preferentially induced apoptosis in human lung cancer cells while sparing normal lung epithelial cells and significantly inhibited the growth of human lung cancer cells as xenografts without apparent adverse effects, suggesting that this combination may have therapeutic value in treating lung cancer.

Answer 6:

**Bibliographic Information**

**Hydroxyurea significantly enhances tumor growth delay in vivo with herpes simplex virus thymidine kinase/ganciclovir gene therapy.** Boucher, P. D.; Ostruszka, L. J.; Murphy, P. J. M.; Shewach, D. S. Department of Pharmacology, University of Michigan Medical Center, Ann Arbor, MI, USA. Gene Therapy (2002), 9(15), 1023-1030. Publisher: Nature Publishing Group, CODEN: GETHEC ISSN: 0969-7128. Journal written in English. CAN 138:117319 AN 2002:513879 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

We have previously demonstrated with several cell lines in vitro that hydroxyurea (HU) synergistically enhances ganciclovir (GCV)-mediated cytotoxicity in bystander cells. In this study, we evaluated the role of DNA synthesis inhibition on enhanced bystander killing and assessed whether addn. of HU would improve the efficacy of the HSV-TK/GCV system in vivo. Compared with GCV treatment alone, addn. of HU resulted in increased DNA synthesis inhibition and delayed progression through S phase following removal of drug. In a xenograft tumor model, 1:10 and 1:1 mixts. of HSVtk- and LacZ-expressing SW620 cells were injected s.c. in the flanks of nude mice and treated i.p. (100 mg/kg GCV, 1500 mg/kg HU) daily for 5 days. Tumors from mice treated with GCV alone grew rapidly and increased to 10 times their initial size in 15.7±1.8 and 16.0±0.9 days for 1:10 and 1:1 mixts., resp. However, when both GCV and HU were administered in combination, a single complete tumor regression was obsd. in both the 1:10 and 1:1 groups. In the remaining mice treated with GCV/HU, it took 23.2±2.1 (1:10) and 26.4±3.8 days (1:1) to obtain a similar 10-fold increase in tumor size.

Answer 7:

**Bibliographic Information**

**2-Benzoxazolyl and 2-benzimidazolyl hydrazones derived from 2-acetylpyridine: a novel class of antitumor agents.** Easmon, Johnny; Puerstinger, Gerhard; Roth, Thomas; Fiebig, Heinz-Herbert; Jenny, Marcel; Jaeger, Walter; Heinisch, Gottfried; Hofmann, Johann. Institute of Pharmacy, University of Innsbruck, Innsbruck, Austria. International Journal of Cancer (2001), 94(1), 89-96. Publisher: Wiley-Liss, Inc., CODEN: IJCNAW ISSN: 0020-7136. Journal written in English. CAN 136:31295 AN 2001:666329 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

Here we describe the effects of novel benzoxazol-2-yl and benzimidazol-2-yl hydrazones derived from 2-pyridinecarbaldehyde and 2-acetylpyridine. The IC50 values for inhibition of cell proliferation in KB-3-1, CCRF-CEM, Burkitt's lymphoma, HT-29, HeLa, ZR-75 and MEXF276L by most of the novel compds. are in the nanomolar range. In colony-forming assays with human tumor xenografts the compds. 2-actylpyridine benzoxazol-2-ylhydrazone (EPH52), 2-acetylpyridine benzoimidazol-2-ylhydrazone (EPH61) and 2-acetylpyridine 1-methylbenzoimidazol-2-ylhydrazone (EPH116) exhibited above-av. inhibition of colon carcinoma (IC50 = 1.3-4.56 nM); EPH52 and EPH116 also exhibited above-av. inhibition of melanoma cells. As shown with human liver microsomes, EPH116 is only moderately metabolized. The compd. inhibited the growth of human colon cancer xenografts in nude mice in a dose-dependent manner. Thiosemicarbazones derived from 2-formylpyridines have been shown to be inhibitors of ribonucleotide reductase (RR). The following results show that RR is not the target of the novel compds.: cells overexpressing the M2 subunit of RR and resistant to the RR inhibitor hydroxyurea are not cross-resistant to the novel compds.; inhibition of RR occurs at 6- to 73-fold higher drug concns. than that of inhibition of cell proliferation; the pattern of cell cycle arrest in S phase induced by the RR inhibitor hydroxyurea is not obsd. after treatment with the novel compds.; and a COMPARE anal. with the related compds. 2-acetylpyrazine benzothiazol-2-ylhydrazone (EPH95) and 3-acetylisoquinoline benzoxazol-2-ylhydrazone (EPH136) showed that the pattern of these compds. is not related to any of the std. antitumor drugs. Therefore, these novel compds. show inhibition of colon cancers and exhibit a novel mechanism of action.

Answer 8:

**Bibliographic Information**

**Triapine (3-aminopyridine-2-carboxaldehyde-thiosemicarbazone): A potent inhibitor of ribonucleotide reductase activity with broad spectrum antitumor activity.** Finch, R. A.; Liu, M.-C.; Grill, S. P.; Rose, W. C.; Loomis, R.; Vasquez, K. M.; Cheng, Y.-C.; Sartorelli, A. C. Cancer Center, Department of Pharmacology and Developmental Therapeutics Program, Yale University School of Medicine, New Haven, CT, USA. Biochemical Pharmacology (2000), 59(8), 983-991. Publisher: Elsevier Science Inc., CODEN: BCPCA6 ISSN: 0006-2952. Journal written in English. CAN 132:288409 AN 2000:127295 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

Previous studies from our labs. have shown that (a) Triapine is a potent inhibitor of ribonucleotide reductase activity and (b) hydroxyurea-resistant L1210 leukemia cells are fully sensitive to Triapine. In an analogous manner, Triapine was similarly active against the wild-type and a hydroxyurea-resistant subline of the human KB nasopharyngeal carcinoma. Triapine was active in vivo against the L1210 leukemia over a broad range of dosages and was curative for some mice. This agent also caused pronounced inhibition of the growth of the murine M109 lung carcinoma and human A2780 ovarian carcinoma xenografts in mice. Optimum anticancer activity required twice daily dosing due to the duration of inhibition of DNA synthesis which lasted about 10 h in L1210 cells treated with Triapine in vivo. DNA synthesis in normal mouse tissues (i.e. duodenum and bone marrow) uniformly recovered faster than that in L1210 leukemia cells, demonstrating a pharmacol. basis for the therapeutic index of this agent. Triapine was more potent than hydroxyurea in inhibiting DNA synthesis in L1210 cells in vivo, and the effects of Triapine were more pronounced. In addn., the duration of the inhibition of DNA synthesis in leukemia cells from mice treated with Triapine was considerably longer than in those from animals treated with hydroxyurea. Combination of Triapine with various classes of agents that damage DNA (e.g. etoposide, cisplatin, doxorubicin, and 1-acetyl-1,2-bis(methylsulfonyl)-2-(2-chloroethyl)hydrazine) resulted in synergistic inhibition of the L1210 leukemia, producing long-term survivors of tumor-bearing mice treated with several dosage levels of the combinations, whereas no enhancement of survival was found when Triapine was combined with gemcitabine or cytosine arabinoside.

The findings demonstrate the superiority of Triapine over hydroxyurea as an anticancer agent and further suggest that prevention by Triapine of repair of DNA lesions created by agents that damage DNA may result in efficacious drug combinations for the treatment of cancer.

Answer 9:

**Bibliographic Information**

**Teratogenic drugs inhibit the differentiation of fetal rat limb buds grafted in athymic (nude) mice.** Shiota, Kohei; Uwabe, Chigako; Yamamoto, Masako; Arishima, Kazuyoshi. Fac. Med., Kyoto Univ., Kyoto, Japan. Reproductive Toxicology (1990), 4(2), 95-103. CODEN: REPTED ISSN: 0890-6238. Journal written in English. CAN 112:229239 AN 1990:229239 CAPLUS

**Abstract**

Forelimb buds of day-14 rat fetuses were cut into pieces and transplanted s.c. into athymic (nude) mice. On the 7th, 9th, and 11th days after grafting, the nude mice were treated with various drugs, including rat teratogens. On the 20th day, the grafted tissue was examd. macroscopically and histol. While control grafts showed substantial growth and tissue differentiation, the differentiation of grafts was inhibited by treatment with 5-fluorouracil, cyclophosphamide, hydroxyurea, cycloheximide, mitomycin C, caffeine, aspirin, retinol palmitate, all-trans-retinoic acid, and ascorbic acid. Hydrocortisone, tetracycline, and thalidomide did not adversely affect the differentiation of grafts. This susceptibility of the transplanted rat limb buds was generally close to the teratol. sensitivity of rat fetuses in vivo. The heterotransplantation method of embryonic tissues may be useful as a new exptl. system in developmental toxicol.

Answer 10:

**Bibliographic Information**

**Chemosensitivity of human head and neck cancer xenografts in the clonogenic assay and in nude mice.** Boerrigter, G. H.; Heinerman, E. C. M.; Braakhuis, B. J. M.; Snow, G. B. Dep. Otalaryngol., Free Univ. Hosp., Amsterdam, Neth. British Journal of Cancer (1986), 54(1), 53-9. CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 105:126666 AN 1986:526666 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

The potential use of human head and neck (H + N) tumors, growing in athymic nude mice, for preclin. assessment of cytostatic drug sensitivity in a soft agar cloning system was examd. Of 20 H + N tumor xenografts, obtained from 6 different xenograft lines, 17 demonstrated sufficient colony growth to evaluate in vitro drug sensitivity. Moreover, all xenografts provided enough cells to test 8 cytostatic drugs at 3 concns. each. A dose-dependent inhibition of colony growth was obtained with all drugs tested, except methotrexate. Tumors were considered sensitive when the drug concn. required to inhibit colony formation by 50%, was less than 1/10 of the peak plasma concn. in patients. All H + N tumor lines were resistant to cisplatin, doxorubicin, hydroxyurea, mafosfamide (an in vitro active analog of cyclophosphamide) and methotrexate. Bleomycin was active in 1/6 and 5-fluorouracil in 6/6 of the H + N tumor lines tested. In 32 cases, the in vitro data of the H + N tumor lines and a chemosensitive rat rhabdomysarcoma were compared directly with in vivo results obtained in nude mice. The clonogenic assay correctly predicted sensitivity in 4/6 (66.7%) and resistance in 21/26 (80.8%) of the cases. A lack of correlation was noted for methotrexate, 5-fluorouracil and cyclophosphamide. In vitro culture of human H + N xenografts may provide a means for a rapid and large scale screening to identify new drugs active against H + N malignancies. In addn., the clonogenic assay may help to select drugs for subsequent testing in the nude mouse xenograft model. The lack of correlation for some drugs in the present study indicates that there are some limitations in the use of xenograft tumor material for in vitro testing of new drugs.

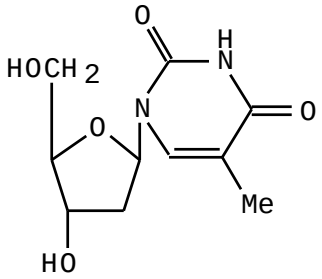
Answer 11:

**Bibliographic Information**

**Experimental therapy of human tumors heterotransplanted in nude mice by continuous infusion of short-acting chemotherapeutic agents.** Lee, Shih Shun; Giovanella, Beppino C.; Stehlin, John S., Jr.; Brunn, Jan C. Stehlin Found. Cancer Res., Houston, TX, USA. Proceedings of the International Workshop on Nude Mice (1982), Volume Date 1979, 3rd(Vol. 2), 657-64. CODEN: PIWMDW ISSN: 0171-1784. Journal written in English. CAN 98:119018 AN 1983:119018 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

A method was developed by which nude mice can be infused continuously with vols. of fluid varying from 0.2 to 1 mL/h for periods of time up to 6 days. The infusion can be repeated after a week's rest for up to 8 times. The method is based on partial restraint of the mouse, which is infused through a fine plastic catheter inserted into the peritoneum or in the s.c. space of the back and attached firmly but elastically to the skin. Animals carrying heterotransplanted human tumors were treated with continuous infusion of thymidine (I) [50-89-5] or hydroxyurea [127-07-1]. The effectiveness of such therapeutic agents can be enhanced if they are administered by continuous infusion instead of single injection.

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Answer 12:

**Bibliographic Information**

**Chemotherapy of cell-line-derived human colon carcinomas in mice immunosuppressed with antithymocyte serum.** Tibbetts, Lance M.; Chu, Ming Y.; Hager, Jean C.; Dexter, Daniel L.; Calabresi, Paul. Dep. Med., Brown Univ., Providence, RI, USA. Cancer (New York, NY, United States) (1977), 40(5, Suppl.), 2651-9. CODEN: CANCAR ISSN: 0008-543X. Journal written in English. CAN 88:115007 AN 1978:115007 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

An in vivo model is described for assessing the antitumor activity of chemotherapeutic agents. Tumors derived from human colon carcinoma cell lines injected into antithymocyte serum (ATS) immunosuppressed mice were used. In this system, both antitumor effects and host toxicity can be quantitated, permitting calcn. of a therapeutic Index. Compared with other xenograft models, the present system is simple. Expts. are completed in less than 2 wk, and the use of cultured cell lines allows in vitro studies to be performed. The in vitro sensitivities of 1 colon cell line to 22 chemotherapeutic agents and of 4 cell lines to 3 agents is reported. Four drugs used in treating colon cancer (mitomycin C [50-07-7], 5-fluorouracil [51-21-8], BCNU [154-93-8], methyl-CCNU [13909-09-6]) showed antitumor activity in vivo in this system. Each had a low therapeutic index.

Answer 13:

**Bibliographic Information**

**Estimation of tumor sensitivity in vitro. II. Solid Ehrlich carcinoma of the mouse and GW 77, a heterotransplanted human carcinoma.** Seidel, Hans J. Inst. Exptl. Pathol., Farbenfabriken Bayer A.-G., Wuppertal/Elberfeld, Fed. Rep. Ger. Zeitschrift fuer Krebsforschung (1970), 74(2), 131-40. CODEN: ZEKBAI ISSN: 0301-1585. Journal written in German. CAN 73:64879 AN 1970:464879 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

**Abstract**

Actinomycin C was the most effective antitumor agent against Ehrlich carcinoma, while both triaziquone and actinomycin C were highly active against GW 77 tumor, a heterotransplanted human carcinoma, and preferentially depressed cytidine incorporation; rubidomycin was inactive against the GW 77 tumor in vivo, but preferentially reduced the incorporation of thymidine-3H in both Ehrlich carcinoma and GW 77 tumor. Cytosine arabinoside and hydroxyurea selectively inhibited thymidine-3H incorporation in the GW 77 tumor, thus inhibiting DNA synthesis. Cytosine arabinoside was active in vivo whereas hydroxyurea was not; no correlation between the in vivo

and in vitro data could be made.

Answer 14:

**Bibliographic Information**

**Hydroxyurea chemotherapy in the treatment of meningiomas**. Newton Herbert B Dardinger Neuro-Oncology Center and Division of Neuro-Oncology, Department of Neurology, The Ohio State University Medical Center, Columbus, Ohio 43210, USA. newton.2@osu.edu Neurosurgical focus (2007), 23(4), E11. Journal code: 100896471. E-ISSN:1092-0684. Journal; Article; (JOURNAL ARTICLE); General Review; (REVIEW) written in English. PubMed ID 17961035 AN 2007636758 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

**Abstract**

Meningiomas are slow growing, extraaxial tumors that derive from the arachnoidal cap cells of the meninges. Resection remains the main modality of treatment and can be curative in some cases. External-beam radiotherapy and radiosurgery can benefit selected patients. The role of chemotherapy continues to be defined, but should be considered for patients with inoperable or frequently recurring meningiomas. Hydroxyurea, an inhibitor of ribonucleotide reductase, is one of the most active agents and is known to induce apoptosis in meningioma cells in vitro and in mouse xenografts. Results of preliminary clinical studies suggest that hydroxyurea has modest activity against recurrent and inoperable meningiomas, and can induce long term stabilization in some patients. However, the results are conflicting and a few clinical trials did not show positive results. Further clinical trials with larger patient cohorts and longer follow-up periods will be necessary to confirm the activity of hydroxyurea.

Answer 15:

**Bibliographic Information**

**Establishment of an in vivo meningioma model with human telomerase reverse transcriptase**. Cargioli Theresa G; Ugur Hasan C; Ramakrishna Naren; Chan Jennifer; Black Peter M; Carroll Rona S Department of Neurosurgery, Brigham and Women's Hospital, Boston, Massachusetts 02115, USA Neurosurgery (2007), 60(4), 750-9; discussion 759-60. Journal code: 7802914. E-ISSN:1524-4040. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 17415213 AN 2007210720 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

**Abstract**

OBJECTIVE: The lack of meningioma models has hindered research on the pathogenesis and treatment of this commonly diagnosed primary brain tumor. Animal models of meningioma have been difficult to develop, especially those derived from Grade I tumors, which display very slow growth rates, senesce at early passages, and infrequently survive as explants in vivo. In this study, the authors report the establishment of two benign immortalized meningioma cell lines, Me10T and Me3TSC, that can serve as useful models of human meningioma. METHODS: Tissue specimens obtained at the time of surgery were cultured in vitro and transduced with human telomerase reverse transcriptase/SV40 large T antigen to establish long-term cell lines. The telomeric activity, growth kinetics, immunophenotype, and karyotyping of the cell lines were investigated. The growth inhibitory effects of the antitumor therapies, hydroxyurea and sodium butyrate, on these cell lines were determined. In addition, immortalized cell lines were implanted subdurally into mice to confirm their ability to form tumors. RESULTS: Two immortalized benign meningioma cell lines, Me10T and Me3TSC, transduced with catalytic subunit human telomerase reverse transcriptase alone or human telomerase reverse transcriptase and SV40 large T antigen, were established. The meningeal phenotype of the established cell cultures and orthotopic xenografts was confirmed by immunostaining. After subdural injection into athymic nude mice, both cell lines formed identifiable tumors with histological features and immunostaining patterns of human meningioma. CONCLUSION: The Me3TSC and Me10T cell lines can serve as useful model systems for biological studies and the evaluation of novel

therapies on meningioma.

Answer 16:

**Bibliographic Information**

**Oxidative DNA damage and repair in a cell lineage model of human proliferative breast disease (PBD)**.
Starcevic Susan L; Diotte Nicole M; Zukowski Kim L; Cameron Mark J; Novak Raymond F Institute of Environmental Health Sciences, Wayne State University, Detroit, Michigan 48201, USA Toxicological sciences : an official journal of the Society of Toxicology (2003), 75(1), 74-81. Journal code: 9805461. ISSN:1096-6080. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written in English. PubMed ID 12805649 AN 2003412422 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

**Abstract**

Oxidative damage to DNA is thought to play a significant role in mutagenesis, aging, and cancer. Sensitivity to oxidative DNA damage and DNA repair efficiency were examined using a series of human breast epithelial cell lines-MCF-10A, MCF-10AT, and MCF-10ATG3B-with progressively elevated Ras protein. Breast epithelial cells were treated with H2O2, in the absence and presence of the DNA-repair inhibitors hydroxyurea (HU) and cytosine arabinoside (Ara-C). DNA strand breaks were assessed by the mean olive tail moment (microm) using the alkaline single-cell gel electrophoresis (Comet) assay. In untreated cells, the mean olive tail moment values were 4.3 +/- 0.7, 8.3 +/- 1.1, and 7.1 +/- 0.6 microm in the MCF-10A, MCF-10AT, and MCF-10ATG3B cells, respectively. Five min H2O2 treatment produced concentration-dependent DNA damage, with the MCF-10A cells most susceptible and the tumorigenic MCF-10ATG3B cells the least susceptible. Treatment with 100 microM H2O2 resulted in approximately 17-, 6-, and 4.5-fold increases in mean olive tail moment values in the MCF-10A, MCF-10AT, and MCF-10ATG3B cells, respectively, compared to untreated cells. The HCC1937 tumor cell line responded in a manner comparable to the MCF-10ATG3B cells treated with H2O2, HU/Ara-C pre-treatment resulted in a approximately 1.5-fold increase in olive tail moment values in all three cell lines. Protein levels of antioxidant enzymes, including catalase, copper/zinc superoxide dismutase (Cu/Zn SOD), and manganese SOD (MnSOD) were determined in order to examine a potential mechanism for increased resistance to H2O2-mediated DNA damage. Levels of these enzymes increased progressively, with highest expression in MCF-10ATG3B cells. Increased cellular resistance also coincided with marked decreases in p53 protein levels. These results demonstrate that, in this cell lineage, sensitivity to oxidative DNA damage by H2O2 decreases with tumorigenicity (i.e., MCF-10A vs. MCF-10ATG3B), and show that DNA repair, altered Ras, and p53 expression, or compensatory mechanisms involving elevated antioxidant enzymes are involved in mediating these effects.

Answer 17:

**Bibliographic Information**

**Eradication of latent Epstein-Barr virus by hydroxyurea alters the growth-transformed cell phenotype**.
Chodosh J; Holder V P; Gan Y J; Belgaumi A; Sample J; Sixbey J W Program in Viral Oncogenesis and Tumor Immunology, St. Jude Children's Research Hospital, Memphis, TN 38105, USA The Journal of infectious diseases (1998), 177(5), 1194-201. Journal code: 0413675. ISSN:0022-1899. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written in English. PubMed ID 9593003 AN 1998253835 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

**Abstract**

The hallmark of infection by human herpesviruses, life-long persistence in the host, is unaffected by current antiviral therapies effective against replication of virus. In vitro studies indicated that low concentrations of the ribonucleotide reductase inhibitor, hydroxyurea, completely eliminated Epstein-Barr virus (EBV) episomes from latently infected Burkitt's lymphoma (BL) cell subsets, providing the first example of chemotherapeutic eradication of a latent herpesvirus from any

cell population. Unlike parental EBV-positive BL cells, virus-free cell progeny from one treated cell line no longer exhibited the malignant phenotype in tumorigenicity assays. Hydroxyurea-treated primary B lymphocytes immortalized by EBV ceased to proliferate as episomes were lost. The altered growth phenotype of both BL cells and immortalized primary B cells suggests that latent EBV is an appropriate and accessible therapeutic target for treatment of some EBV-induced lymphoproliferations.

Answer 18:

**Bibliographic Information**

**Selective uptake of toxic nucleoside (125IUdR) by resistant cancer**. Bagshawe K D; Sharma K; Southall P J; Boden J A; Boxer G M; Patridge T A; Antoniw P; Pedley R B Department of Medical Oncology, Charing Cross and Westminster Medical School, London, UK The British journal of radiology (1991), 64(757), 37-44. Journal code: 0373125. ISSN:0007-1285. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 1998836 AN 91152395 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

**Abstract**

We report uptake of a thymidine analogue 125-Iodine-5-iodo-2'-deoxyuridine (125IUdR) by nude mice bearing human xenografts of choriocarcinoma or colonic cancer. When 125IUdR was given alone, uptake by intestinal tissues was 5-10 times greater than by the tumours as measured by tissue gamma counting. This ratio was reversed when hydroxyurea or cytosine arabinoside were used as inhibitors of ribonucleotide reductase and were given in combination with 5-fluorouracil or methotrexate to inhibit thymidine synthesis shortly before injecting 125IUdR. Counting the radioactivity in tissues removed 24 hours after 125IUdR gave tumour to highest normal tissue ratios of up to 15:1, but the corresponding nuclear grain counts, which is probably a more reliable indicator of selective uptake into DNA, were in excess of 100:1. The addition of unlabelled IUdR to the regimen only reduced the uptake of 125IUdR when given in relatively large amounts. For this approach to be exploited it is concluded that the tumour must be resistant at the cell level to the inhibitor of DNA synthesis either de novo or as a result of prior exposure to it. This inhibitor can then be used to block uptake of the potentially toxic nucleoside analogue by normal renewal tissues while it is taken up by the resistant cancer cells. By inhibiting synthesis of the corresponding normal nucleosides with inhibitors to which the cancer cells are not resistant, incorporation of the toxic analogues into tumour DNA was enhanced. Although 125IUdR is a convenient agent for exploring this approach and is highly cytotoxic when incorporated in DNA, the clinical potential of reverse role chemotherapy probably lies with the development of toxic non-radioactive nucleoside analogues.

Answer 19:

**Bibliographic Information**

**A cytotoxic DNA precursor is taken up selectively by human cancer xenografts**. Bagshawe K D; Boden J; Boxer G M; Britton D W; Green A; Partridge T; Pedley B; Sharma S; Southall P British journal of cancer (1987), 55(3), 299-302. Journal code: 0370635. ISSN:0007-0920. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 3567064 AN 87185223 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Answer 20:

**Bibliographic Information**

**Effects of hydroxyurea pretreatment of donor rats on growth of haematopoietic diffusion chamber colonies in mice**. Ben-Ishay Z; Sharon S Scandinavian journal of haematology (1977), 18(3), 226-34. Journal code: 0404507. ISSN:0036-553X. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 322255 AN 77150530

**Abstract**

A single dose of hydroxyurea (HU) (400 mg/kg body weight) was injected i.p. into rats. Hydroxyurea, a potent DNA synthesis inhibitor, killed bone marrow cells in the S-phase of the cell cycle. 9-10 h after HU administration, the rat bone marrow contained large numbers of necrotic cells and appeared predominantly lymphoid. Within 24-48 h of HU injection, resumption of normal haematopoiesis was observed. Rat bone marrow, 9-10 h following HU administration, was implanted in peritoneal diffusion chambers (DC) in irradiated mice. The results obtained suggest that pretreatment of donor rats with HU increases the bone marrow content of progenitor cells. The stem cell-enriched marrow was conductive to enhanced growth of DC colonies in irradiated mice.

Answer 21:

**Bibliographic Information**

**Drug-tumor sensitivity matching procedure using diffusion chambers in vivo**. Cain B F; Calveley S B; Boreham B A; West C; Price N A; Walker D J; Churchouse M J Cancer chemotherapy reports. Part 1 (1974), 58(2), 189-205. Journal code: 7607105. ISSN:0069-0112. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 4857364 AN 74170356 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))